Treatment of Hypercalcemia Secondary to Parathyroid Carcinoma with a Novel Calcimimetic Agent

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ABSTRACT

Parathyroid carcinoma is one cause of primary hyperparathyroidism, a condition in which there is hypercalcemia and dysregulated hypersecretion of PTH. In normal, and in some neoplastic parathyroid cells, PTH secretion is mediated by the cell surface calcium-sensing receptor. We describe the first therapeutic use of a novel molecule, a calcimimetic, that has agonist action at the calcium-sensing receptor.

A 78-yr-old man with parathyroid carcinoma was admitted with hypercalcemia, markedly elevated PTH, and a change in mental status. He was treated for 17 days with conventional therapy, which included saline hydration, furosemide, pamidronate, and calcitonin. This was ineffective, and on hospital day 18, calcimimetic at a dose of 50 mg, orally, every 6 h was added. On hospital day 25, the dose was increased to 100 mg, orally, every 6 h, and on hospital day 30, saline and furosemide were discontinued. He was discharged on hospital day 40. With several dose adjustments, he has been treated with mono-

therapy calcimimetic for over 600 days and has not required any other interventions for his parathyroid carcinoma.

Mean daily precalcimimetic treatment values of serum ionized calcium and PTH were 1.83 mmol/L and 872 pg/mL, respectively. During hospitalization, at the lower dose of calcimimetic, calcium and PTH decreased to 1.67 mmol/L and 538 pg/mL; with the higher dose they further decreased to 1.51 mmol/L and 444 pg/mL. Since discharge, and despite increasing levels of PTH, serum calcium has remained high, but lower than the admission level and acutely responsive to changes in calcimimetic doses.

This compound, a calcimimetic, the first of a new class of compounds with activity at the calcium-sensing receptor, has been used to treat a patient with parathyroid carcinoma. During 2 yr of treatment, no adverse clinical effects have been observed, and it appears to have been effective at controlling hypercalcemia. (*J Clin Endocrinol Metab* **83**: 1083–1088, 1998)

P ARATHYROID carcinoma is a rare cause of primary hyperparathyroidism in which there can be marked elevations of PTH and serum calcium (1). Early surgery offers the only chance for cure. Complete surgical resection, however, is usually not possible, and recurrence is common. Medical therapies to treat this and other forms of primary hyperparathyroidism are directed at target tissue actions of PTH, such as osteolysis (2). None is directed at the underlying cause of the hypercalcemia, namely hypersecretion of PTH.

PTH secretion is negatively regulated by increasing serum ionized calcium concentrations (3), a regulation that is largely preserved by neoplastic parathyroid cells, at least in the case of benign tumors (4). Although the precise mechanism of calcium regulation of PTH secretion is not fully understood, identification and characterization of the parathyroid cell calcium-sensing receptor have provided insight about the first step of this pathway (5). The nucleotide sequence of the calcium-sensing receptor predicts seven hydrophobic transmembrane domains similar to other recep-

tors in the G protein-coupled serpentine receptor superfamily, a large extracellular domain with potential calcium-binding clusters of acidic residues, and an intracellular tail (5). Similar or identical calcium receptors have been identified on some other cells known to be involved in calcium homeostasis, such as calcitonin-producing C cells of the thyroid (6) and renal tubular cells (7). Furthermore, the calcium-perturbing role of inactivating mutations, in the case of familial hypocalciuric hypercalcemia and severe neonatal hyperparathyroidism (8), and activating mutations, in the case of familial hypocalcemia with hypercalciuria (9), suggest that agonists and antagonists of this receptor have the potential to modulate PTH levels and, thus, calcium metabolism.

An allosteric modulator of the receptor that has calcimimetic properties has been developed (10) and has entered early clinical trials for the treatment of primary and secondary hyperparathyroidism. Preclinical data showed that this compound (*N*-[1(*R*)-(3-methoxyphenyl)ethyl]-3-(2-chlorophenyl)-1-aminopropane) is effective in lowering both serum ionized calcium and PTH in normal and uremic rats (11). In normal human subjects, single doses decreased PTH levels in a dose-dependent manner, and in a 2-week trial, there was a sustained reduction in serum calcium levels (data on file at Amgen, Thousand Oaks, CA). Single doses of the drug decreased PTH concentrations in patients with primary hyperparathyroidism (12).

These data suggested that this drug may be effective in treating primary hyperparathyroidism.

This report describes the first therapeutic use of this drug, a calcimimetic with activity at the calcium-sensing receptor. It was used to treat a 78-yr-old man with parathyroid carcinoma, the form of primary hyperparathyroidism that is most refractory to treatment.

Case Report

History

The patient was 78 yr old when admitted to the NIH in 1995. He presented in 1988 with hypercalcemia and hyperparathyroidism. Neck exploration was performed, and a solitary tumor was resected. Immediately after the surgery, PTH levels returned to the normal range, and he became eucalcemic. However, 4 yr later, hypercalcemia recurred. He subsequently underwent four additional neck explorations. The patient was transiently eucalcemic after the first three operations, but not after operation 4 or 5. Resected parathyroid tissue from the first three operations was reported as "hyperplastic parathyroid tissue". However, tissue from the last two operations was consistent with parathyroid carcinoma. Over the last several years, his condition gradually worsened; he developed nephrolithiasis with renal insufficiency, osteopenia, anemia, lethargy, and a decline in functional capacity. Before transfer to the NIH, he was being treated as an in-patient at another facility. Treatment there for hypercalcemia included iv hydration and iv pamidronate, neither of which was effective at significantly lowering serum calcium concentrations. Given the degree of renal impairment at baseline, gallium nitrate and mithramycin were not used.

Measurements

Serum for PTH and calcium determinations during the in-patient treatment phase of therapy were drawn each morning approximately 2 h after drug administration. During chronic therapy, blood samples were taken between 1–4 h after drug administration. Serum ionized calcium (Nova, Waltham, MA) and total calcium (Hitachi-Boehringer Mannheim, Indianapolis, IN) were measured using standard techniques. PTH was measured using an immunoradiometric assay (13).

Twenty-four-hour urine specimens were analyzed for calcium using atomic absorption spectrophotometry and for creatinine using standard autoanalyzer techniques.

Acute treatment

On admission to the NIH, the patient was delirious, with marked hypercalcemia and multiple laboratory abnormalities (Table 1). The initial plan on admission was to localize parathyroid tissue and perform a neck exploration to remove PTH-producing tissue. However, five previous neck explorations and the patient's generally debilitated state made the risk of an additional surgery unacceptably high. For that reason the use of the calcimimetic agent was pursued. For the first 18 hospital days, he was treated with conventional therapy. This consisted of hydration with normal saline (175 cc/h, iv) plus furosemide (40 mg, iv, twice daily) from the time of admission. He subsequently received three doses of pamidronate (60 mg each, iv), on hospital days 1, 7, and 10, and salmon calcitonin (100 IU, sc, daily) on hospital days 11–16. Studies to localize parathyroid tissue revealed [131I]sestamibi uptake in the neck without any evidence of metastases outside that region (not

shown). The patient was enrolled in a single use protocol approved by the institutional review board.

The calcimimetic agent (N-[1(R)-(3-methoxyphenyl)ethyl]-3-(2-chlorophenyl)-1-aminopropane) at a dose of 50 mg, orally, every 6 h was added to saline hydration and furosemide on hospital day 18. After 7 days, the dose was increased to 100 mg, orally, every 6 h, and after 7 days at this dose, saline hydration and furosemide were discontinued. The last 9 days of in-patient treatment consisted of monotherapy with calcimimetic.

Acute treatment response

Serum calcium. Despite aggressive conventional therapy, the serum calcium level was very high and variable (Fig. 1), and the patient did not improve clinically. It was not until the calcimimetic was added to his medical regimen that a significant and sustained improvement was seen in serum calcium concentrations. By the second day of treatment, a decrease in the ionized calcium concentration was observed (Fig. 1). The patient began to improve clinically by the third day of treatment, demonstrating improved orientation and increased appetite. On hospital day 25, the dose of calcimimetic was increased to 100 mg, orally, every 6 h; with this dose increase, there was a further decrease in ionized calcium (Fig. 1). After 7 days at the higher dose, saline hydration and furosemide were discontinued. Medical therapy at this point consisted only of the calcimimetic. Serum calcium concentrations remained stable on calcimimetic monotherapy (Fig. 1).

Serum PTH. There was a variable change in the PTH level acutely in response to calcimimetic administration, but with an overall trend downwards (Fig. 2a). The downward trend in PTH is demonstrated by the average daily PTH concentration (Fig. 2b). There were dramatic, if unsustained, decreases in PTH with both the first administration of the calcimimetic on day 18 and the doubling of the dose on day 25 (Fig. 2b).

Urinary calcium. Averages of daily urinary calcium excretion, based on 24-h urine collections, are shown (Fig. 3). Urinary calcium excretion was quite high during conventional therapy (saline, furosemide, pamidr-

**BLOOD IONIZED CALCIUM IN RELATION
TO CALCIMIMETIC THERAPY FOR
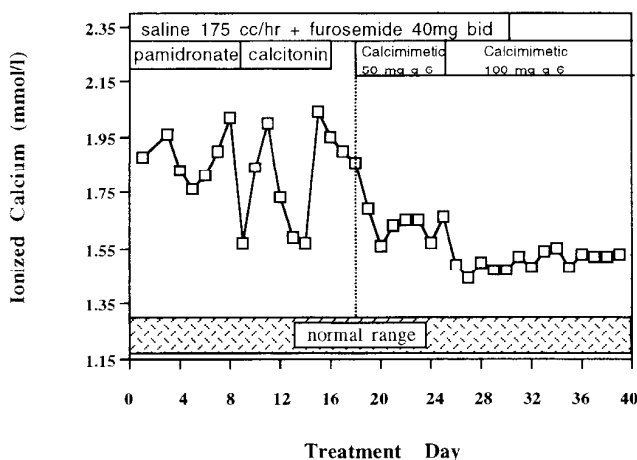PARATHYROID CANCER**

Treatment Day

FIG. 1. Daily ionized calcium concentrations during hospitalization. Ionized calcium was measured each morning 2 h after administration of the drug. The medical treatment the patient was receiving is represented across the *top* of the figure. Saline and furosemide at the doses indicated were administered continuously from days 1–30. Pamidronate at a dose of 60 mg was administered iv on days 1, 7, and 10. Salmon calcitonin at a dose of 100 IU was administered sc daily on days 11–16. Day 18 represents the first day of treatment with the calcimimetic drug. The calcimimetic (100 mg, orally, every 6 h) was the only therapy for the last 7 days of hospitalization.

TABLE 1. Clinical data

Parameter	Normal range	Admission (day 1)	Discharge (day 40)
Ionized calcium (mmol/L)	1.17–1.31	1.96	1.53
PTH (pg/mL)	9.4–49	1128	357
Creatinine (mg/dL)	0.9–1.4	2.3	2.2
Creatinine clearance (mL/min)	90–125	30	29
Hematocrit (%)	36–48	21	27
Albumin (g/dL)	3.7–4.7	2.6	3.9

PTH IN RELATION TO CALCIMIMETIC
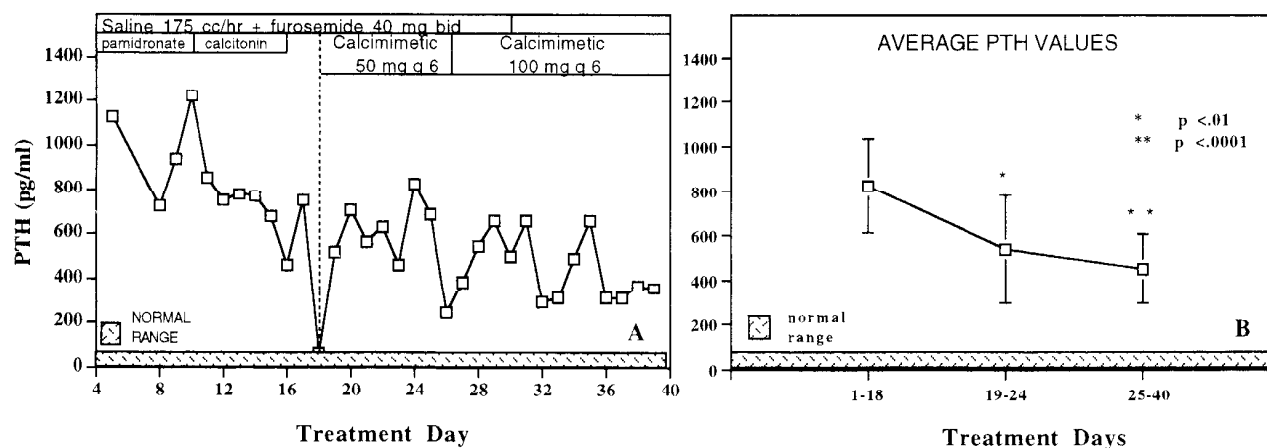## THERAPY FOR PARATHYROID CANCER

FIG. 2. PTH in relation to calcimimetic in therapy for parathyroid cancer. A, Serial PTH values. PTH was measured every day 2 h after drug administration. Treatment is represented across the *top* of the figure. Saline and furosemide at the doses indicated were started on the day of admission and continued until day 30. Pamidronate at a dose of 60 mg was administered iv on days 1, 7, and 10. Calcitonin (100 IU) was administered sc daily on days 11–16. Calcimimetic at the doses indicated was started on day 18 and continued until discharge on day 40. The precipitous decrease in PTH on day 18 followed the initial administration of calcimimetic. B, Average daily PTH values. Average daily PTH concentrations during the various treatment regimens with SEs are shown. PTH was measured at each morning 2 h after administration of the drug. The *P* values refer to the difference between the treatment dose and the baseline. The treatment on days 1–18 consisted of saline, furosemide, pamidronate, and calcitonin. On days 18–24, the treatment was furosemide, saline, and calcimimetic (50 mg, orally, every 6 h). Treatment on days 25–40 was calcimimetic (100 mg, orally, every 6 h) plus furosemide and saline for the first half of those days.

onate, and calcitonin). With the addition of calcimimetic to the conventional therapy, there was a decrease in urinary calcium excretion form baseline that was statistically significant at the higher dose of calcimimetic. Furthermore, there was a statistically significant decrease in urinary calcium excretion between the lower dose of calcimimetic (plus saline and furosemide) and the higher dose of calcimimetic (plus saline and furosemide). When saline and furosemide were removed from the medical regimen, and the treatment was calcimimetic alone at 100 mg, orally, every 6 h, there was a dramatic decrease in urinary calcium excretion to just above the normal range.

Clinical status. The biochemical response was paralleled by a clinical improvement. The patient's sensorium cleared, appetite returned, and there was improvement in serum albumin and weight.

Chronic treatment

The patient was discharged on treatment day 40, receiving calcimimetic at a total daily dose of 400 mg (100 mg, orally, 4 times daily). Approximately 1 month after discharge, his serum calcium level returned to the normal range, and the dose was decreased to 200 mg/day. Subsequent increases in serum calcium and PTH prompted several dose increases. At this writing, the patient is 80 yr old and has been treated with calcimimetic continuously for over 21 months.

Chronic treatment response

Serum calcium. Serum calcium values fluctuated over the course of chronic treatment (Fig. 4a). After approximately 1 month of treatment, while the patient was taking 400 mg/day of the calcimimetic, serum calcium fell into the normal range. This prompted a decrease in the dose of calcimimetic to 200 mg/day to avoid hypocalcemia. Subsequently, serum calcium rose to 2.95 mmol/L (normal range, 2.05–2.50 mmol/L), and the dose of calcimimetic was increased to 300 mg/day. This resulted in decreases in both serum calcium and PTH that were only temporarily sustained (Fig. 4, a and b). Serum calcium rose to 2.98 mmol/L, and the dose of calcimimetic was increased to 350 mg/day. There was a transient decrease in serum calcium, but by day 104, serum calcium had increased

to 2.98 mmol/L, and the dose of calcimimetic was increased to 400 mg/day. For approximately the next 100 days, serum calcium was relatively stable but eventually rose to 3.25 mmol/L, necessitating an increase in the calcimimetic dose to 600 mg/day. For approximately the last year he has continued to receive this dose. Although there have been fluctuations in serum calcium levels, he has remained stable clinically.

Serum PTH. There have been wide variations and a slowly progressive rise in PTH values over the more than 600 days of treatment (Fig. 4b). Of note, however, is the response of PTH to several of the dose adjustments. With the initiation of calcimimetic on day 18, and with the dose increases on days 90, 104, and 222, there was a marked decrease in PTH. Furthermore, a time-course study performed approximately 2 months into treatment demonstrated that a single 50-mg dose of the drug was able to decrease serum PTH concentrations from 1655 pg/mL at baseline to 870 pg/mL 1 h after treatment, a 47% reduction. Serum PTH values rose to 1185 pg/mL 2 h after the 50-mg dose, a 29% decrease from the baseline. However, there continues to be a steady rise in PTH with the passage of time.

Other clinical indicators. Clinically, the patient has done well over the period of treatment. Except for the brief period of delirium and decompensation at admission and despite almost 10 yr of severe hyperparathyroidism, he remains highly functional. He is 80 yr old, working full time, and reports feeling well. Since discharge form our facility, he has not required medications other than the calcimimetic for the treatment of hyperparathyroidism or hypercalcemia. In addition, all measures of renal, cardiac, hepatic, hematological, and pancreatic functioning have remained stable over the entire treatment period (not shown). Serum 25 and 1,25-hydroxyvitamin D levels were normal at baseline and have remained essentially unchanged throughout treatment (not shown). He has had no complaints and has not experienced any side-effects that can be ascribed to treatment with the calcimimetic.

Discussion

This single patient study demonstrates the probable efficacy and lack of adverse clinical effects in 2 yr of treatment

FIG. 3. Urinary calcium during the various treatments. The mean and SE of daily 24-h urine collections during the various treatments are shown for the first 40 days of treatment. Treatment during the various periods are as follows: days 1–17, saline hydration (175 cc/h), furosemide (40 mg, iv, twice daily), and pamidronate (60 mg, iv on days 1, 7, and 10) and salmon calcitonin (100 IU, sc, daily on days 11–16); days 18–24, saline hydration and furosemide at the doses above plus calcimimetic (50 mg, orally, every 6 h); days 25–29, saline hydration and furosemide at the doses above plus calcimimetic (100 mg, orally, every 6 h); and days 30–39, calcimimetic alone (100 mg, orally, every 6 h). Urinary calcium decreased during each phase of treatment. There was a statistically significant decrease in urinary calcium from baseline when the dose of calcimimetic (with saline and furosemide) was increased to 100 mg, orally, every 6 h. Also, urinary calcium decreased significantly when the dose of calcimimetic was increased from 50 to 100 mg, orally, every 6 h. When saline and furosemide were discontinued, urinary calcium dropped to just above the normal range.

URINARY CALCIUM DURING VARIOUS TREATMENTS IN PARATHYROID CARCINOMA
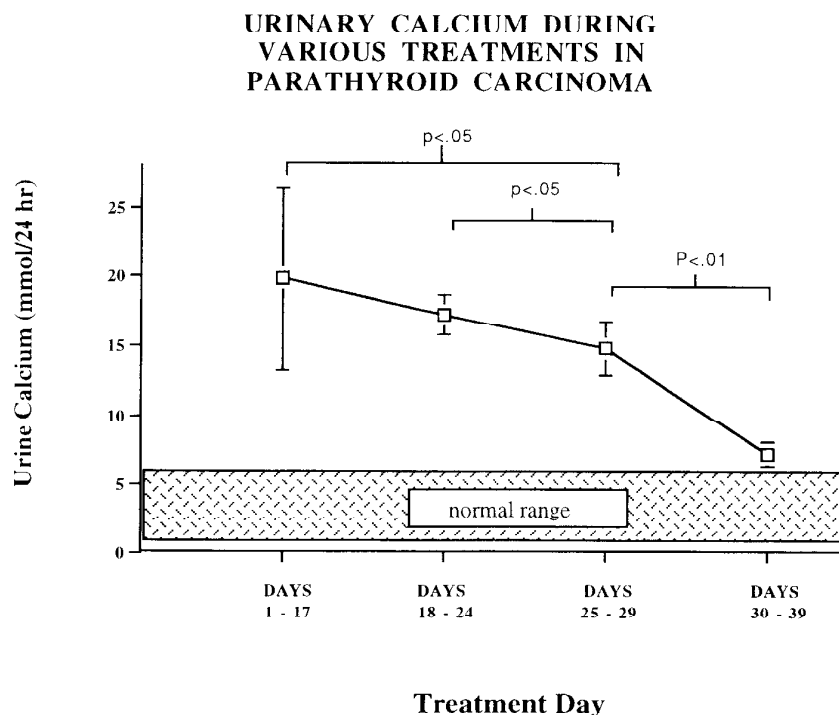
Treatment Day

of a patient with parathyroid carcinoma with a novel calcimimetic. The patient had been progressively deteriorating for 1.5 yr before treatment with calcimimetic, with worsening hypercalcemia and declining functional status to the point where he was moribund on admission. Acutely, there was a marked decline in serum calcium after the administration of calcimimetic. This was paralleled by a decrease in average daily PTH values. There is a possibility that the acute response in serum calcium and PTH was not so much the result of the calcimimetic, but, rather, the cumulative effect of the conventional therapies. This seems unlikely because the patient had been treated with conventional therapy on a number of occasions just before admission without a similar effect. Furthermore, although conventional therapies can lower serum calcium, the indirect effect at the level of the parathyroid gland is to increase, not decrease, serum PTH. The temporal relationship to drug administration, the dose-response effect, and the sustained effect with the discontinuation of saline and furosemide all point to the likelihood that the calcimimetic was the cause of the acute and sustained decline seen in serum calcium over the first 40 days of treatment.

The acute response in PTH is not as clear-cut as the response of calcium. However, when the daily PTH values are pooled and averaged, a dose-dependent decrease, paralleling the decrease in serum calcium, is observed. The wider variability in PTH values is probably a result of the minute to minute fluctuations that can take place in serum PTH values (14).

The effect of calcimimetic on urinary calcium is difficult to interpret. With the addition of calcimimetic to conventional therapy, there was a statistically significant decrease in urinary calcium. With calcimimetic as monotherapy, there was a marked reduction in urinary calcium excretion. Activation of the calcium receptor in the kidney of patients with activating mutations produce hypercalciuria (9). Therefore, an exogenous activator of the receptor would be expected to raise urinary calcium. In fact, hypercalciuria would be a concern in the administration of this class of drug. The decrease in urinary calcium most likely reflects the net effect of the complex interaction of competing regulators of urinary calcium. As serum calcium is lowered, the load of calcium filtered by the kidney is decreased. This is probably the reason why there was a decrease in urinary calcium with the addition of calcimimetic. There was no difference in the fractional excretion of calcium between when the patient was receiving conventional therapy only and when the drug was added to conventional therapy or with an increase in the dose of the drug (data not shown). With the discontinuation of furosemide and saline, there was a significant decrease in the fractional excretion of calcium. Therefore, it is not likely that a drug effect by the calcimimetic on the fractional excretion of calcium is the cause of the changes in urinary calcium. When furosemide was stopped, there was a further marked reduction in urinary calcium, probably the result of withdrawal of the loop diuretic. In view of the theoretical concerns raised above, it is comforting to see that there is not marked hypercalciuria. It is not unreasonable to expect this degree of hypercalciuria in a patient with his level of hypercalcemia even in the presence of impaired renal function. Elucidation of the interacting mechanisms would require measurements with and without the drug. Given the severity of the patient's disease, it would not be ethical to discontinue the drug.

SERUM CALCIUM AND PTH IN
PRATHYROID CANCER DURING LONG
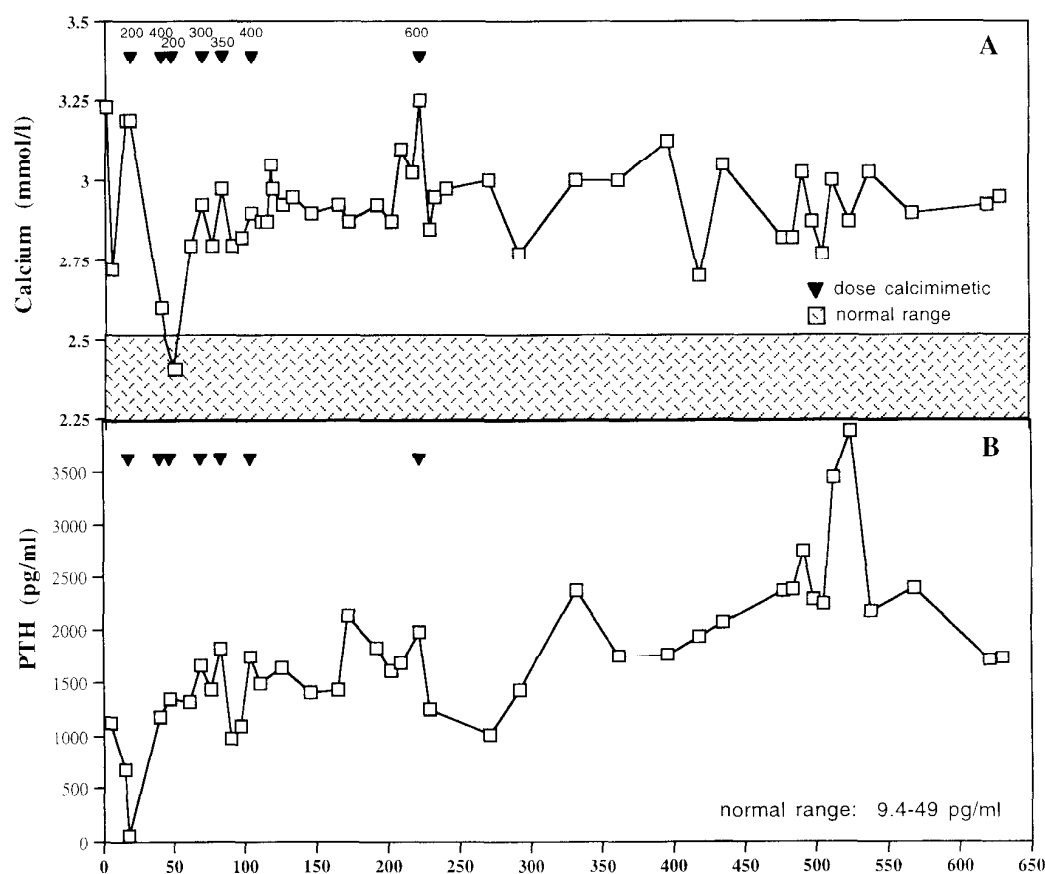## TERM ADMINISTRATION OF CALCIMIMETIC

FIG. 4. Serum calcium and PTH during treatment with calcimimetic in parathyroid cancer. A, Serial serum calcium measurements. Serum calcium was measured throughout the course of treatment. Dose changes in calcimimetic are indicated with *black arrowheads* across the *top* of the figure. Of note are the dramatic decreases in serum calcium noted with first dose of calcimimetic on day 18 and with several subsequent dose increases (350 and 600 mg). B, Serial serum PTH measurements. Serum PTH was measured during chronic administration of calcimimetic in a patient with parathyroid cancer. The first dose (50 mg, orally, every 6 h) was administered on day 18. Subsequent dose changes are illustrated across the *top* of the figure and are indicated by the *black arrowheads*. Dose changes correlate to transient changes in PTH values, but the overall trend of PTH, despite dose increases, is upward.

During almost 2 yr of calcimimetic treatment, serum calcium has remained relatively stable. This is dramatically different from what occurred in the 1.5 yr before starting this therapy, when progressively worsening hypercalcemia became life threatening. The stabilization of serum calcium has occurred without the addition of other therapies. This may reflect the effect of the calcimimetic. Proof of this, however, would require stopping and restarting the drug, a course that is not appropriate in this case.

The response of PTH to the chronic administration of calcimimetic is less clear. The PTH level has had some of the predicted acute responses to the administration of a calcimimetic; *i.e.* with a dose decrease on day 47, PTH rose, and with dose increases on days 83, 104, and 222, PTH decreased. However, over the long term there has been a steady rise in

the PTH. This is not surprising given the nature of the disease. Parathyroid carcinoma is the most severe and aggressive form of primary hyperparathyroidism and often loses responsiveness to interventions to which less severe forms of primary hyperparathyroidism respond (1). The escape of responsiveness to the calcimimetic could be explained by a number of scenarios, including further dedifferentiation of the cancer, increased growth of the tumor, or tumor metastases.

Perhaps the most surprising aspect of the patient's response is the maintenance of a relatively stable serum calcium level in the face of an increasing serum PTH level. As the drug is apparently becoming less effective at the level of the parathyroid cell, one would have to evoke either renal or bone effects of the drug to explain this. The observations that

there was a significantly higher level of urinary calcium during conventional therapy and that the level of urinary calcium decreased when the dose of calcimimetic was increased, suggest that an increase in urinary calcium secretion is not an explanation of the major mechanism of the drug. However, this remains to be studied in a more direct and controlled fashion. An effect of the calcimimetic on bone would be a plausible explanation of the lack of an increase in serum calcium in the face of increasing PTH. It is possible that the calcimimetic is inhibiting PTH action on bone via its action on the calcium-sensing receptor. There are reports that demonstrate the presence of the calcium receptor in chondrocytes (15, 16) and a recent report demonstrating the presence of the receptor in human and mouse bone marrow cells with osteogenic potential (17). In addition, there is evidence for a molecularly distinct calcium-sensing receptor present in a murine-derived osteoblast cell line (18) at which this compound could potentially have action.

Inhibition of osteoclastic bone resorption would explain a lack of increase in serum calcium. However, this is not likely either, given that there has been a steady decline in bone density at all sites in serial measurements of bone density. In 1 yr of calcimimetic therapy, bone density at the spine, hip, and radius decreased 11%, 13%, and 19%, respectively. This indicates that osteoclastic activity is intact, and that decreased osteoclastic activity is not the cause of the lack of increase in serum calcium. An alternative explanation would be that the tumor is now secreting a PTH molecule that is detected by the intact PTH assay but is less biologically active.

No adverse effects have been observed during the 2 yr of administration of this drug. This elderly and very ill patient has tolerated treatment well. All measures of hepatic, renal, gastrointestinal, pulmonary, and cardiac function have been stable. In fact, the patient, despite his age and now almost 10 yr of primary hyperparathyroidism (including parathyroid carcinoma), continues to work full time and generally feels well. The patient's grave condition at presentation, the severity of his underlying disease, and his lack of responsiveness to conventional therapy all justified the use of this new drug. However, these same factors do not allow for the ideal study to prove efficacy or to delineate mechanisms of action. Given these limitations, we are able to say that the drug has caused no adverse clinical effects and that it is probably effective at controlling PTH-mediated hypercalcemia in this case of parathyroid carcinoma. Although the results in this patient were clinically dramatic and biochemically encouraging, further research will be required to establish the safety, efficacy, and mechanism of this class of compound in treating PTH-mediated hypercalcemia.

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